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U.S. Pharmacopeial Convention

Excipient Stakeholder Forum Updates
Stakeholder Forum Progress and Achievements

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Excipient Stakeholder Forum Purpose

Overarching Purpose…

- To provide a forum for manufacturers, distributors, and users of excipients to discuss key issues/topics in an open forum setting.
- To encourage excipients constituencies to work openly and directly with USP as well as collaborate with fellow stakeholders.

Specifically…

- *Extending opportunities* for participation to a broad range of excipients stakeholders
  - ensures industry-wide input to USP
  - further understand excipient issues that will facilitate update and development of excipient monographs.
- *Educating stakeholders* on USP activities and initiatives that might affect excipients stakeholders,
  - e.g., *USP/NF* standard setting process, harmonization, Global Education, and Verification programs.

Recap: Excipient Stakeholder Forum meetings

First Meeting:

June 7, 2013 all day in person and WebEx

Second Meeting:

June 18, 2014 all day in person and WebEx

Third Meeting:

September 29, 2016 half-day webinar

Progress to date: Major topics covered–Meeting 1

The USP Excipients Stakeholder Forum
Meeting #1 for 2010-2015
Friday, June 7, 2013
Spalding Auditorium
USP Headquarters, Rockville, Maryland and via Webex
Priscilla Zawislak, IPEC-Americas, Chair

Agenda

Goals and Expected Outcomes

1. Provide overview of USP and its standards for excipients for new participants
2. Provide updates on excipients topics of interest
3. Receive stakeholder feedback on excipient and related standards

7:30 a.m.	**Registration and Information, Continental Breakfast**	
8:00 a.m.	**1. Opening and Introductory Remarks**	
	a. Opening and Introduction	Mario Sindaco
	b. Call to Order	Priscilla Zawislak
	c. Welcome	Roger Williams
8:15 a.m.	**2. Elemental Impurities**	
	a. USP Elemental Impurities Update	Roger Williams
	b. Discussion	
8:45 a.m.	**3. USP and FDA Excipient Activities**	
	a. USP's Global Science and Standards Division	Srini Srinivasan
	b. USP Excipients Standards-setting Process	Catherine Sheehan
	c. FDA Perspective on Excipient Quality	Steve Wolfgang
	d. USP Spectral Library Updates	Bei Ma/Michael Dotlich
	e. Discussion	
10:00 a.m.	**Break**	
10:15 a.m.	**4. Excipient Stakeholder Roundtable**	Stakeholders
	Each stakeholder group will provide a five-minute overview of their organizations and interests in USP standards followed by general discussion	
11:00 a.m.	**5. Excipient Monograph Modernization**	Lawrence H. Block
12:00 p.m.	**Lunch**	
1:00 p.m.	**6. Excipient Monographs in the *Medicines Compendium***	
	a. *Medicines Compendium* Overview	Todd Cecil
	b. Excipients in the *Medicines Compendium*	Jiasheng Tu
	c. Discussion	
1:45 p.m.	**7. Excipient Related General Chapters**	Catherine Sheehan
2:45 p.m.	**8. Pharmacopeial Education**	Peihong Liang
3:00 p.m.	**9. Next Steps, Closing Remarks**	Priscilla Zawislak

The USP Excipients Stakeholder Forum
Meeting #2 for 2010-2015
Wednesday, June 18, 2014
9:00 a.m.-3:50 p.m.
Spalding Auditorium
USP Headquarters, Rockville, Maryland and via Webex
Steve Boudreau, Chair

Agenda

8:30 a.m.	Registration and Information, Continental Breakfast	
9:00 a.m.	1. Opening and Welcome	Mario Sindaco/Steve Boudreau
9:10 a.m.	2. General USP Updates	
	a. CEO Introduction	Ron Piervincenzi
	b. 2015 USP Convention	Joe Moerke
	c. Call for Candidates	Mario Sindaco
	d. Global Education and Training	Christine Lau
	e. Discussion	
10:00 a.m.	3. USP and FDA Excipient Activities	
	a. USP Overview	Srini Srinivasan
	b. USP Excipients Standards-setting Process	Catherine Sheehan
	c. Planning Committee Introduction and Background	Planning Committee Members
	Each stakeholder group on the Planning Committee will provide a five-minute overview of their organizations and interests in USP standards	
	d. FDA/USP Spectral Library Updates	Steve Wolfgang/Bei Ma
	e. FDA/Inactive Ingredient Database Updates	Naiqui Ya
	f. Discussion	
11:15 a.m.	Break	
11:30 a.m.	4. Excipient Monograph Modernization	
	a. USP Priority Excipient Monograph Modernization updates	Catherine Sheehan
	b. EP Perspective: How to Develop/Update an Excipient Monograph	Lore Vignoli
	c. FDA Monograph Modernization initiative	Steve Wolfgang
	d. Gelatin NF Identification Test Update	
	i. GMIA Manufacturers Perspective	Dean Wood
	ii. Gelatin Capsules Manufacturers Perspective	Steven Leinbach
	iii. USP Update on Gelatin Capsules, New Monographs, and Dissolution Chapter	Margareth Marques
	iv. Discussion: Gelatin and Gelatin Capsule Quality Challenges	
12:00 p.m.	Lunch	
1:00 p.m.	4. Excipient Monograph Modernization (cont.d)	
2:00 p.m.	5. Standards Acquisition and Its Role in the Donor Recognition Program	Donna Kaye Wilson
2:20 pm	6. Stakeholder Roundtable Discussion	Mark Empie, Bob King, David Schoneker, Lore Vignoli, Bill Lamb
	Challenges to modernization and harmonization of USP-NF monographs when FCC and CFR specifications exist (Speakers - five speakers representing industry makers, pharmaceutical users, distributors, and FDA, followed by open discussion)	
3:20 p.m.	7. USP Verification program	John Atwater
3:50 p.m.	8. Next Steps, Closing Remarks	Steve Boudreau

Progress to date – Major topics covered: Meeting 2

Meeting 2 topics addressed key issues identified through its stakeholders during the discussion

- Industry & regulatory agencies are working together- utilizing and sharing each others resources, experience and knowledge in the development/strengthening of compendial standards.
- The European Pharmacopoeia provided an update on the standards setting process for *Ph. Eur.*
- FDA recommended USP to consider adding a new analytical test or tests to the Gelatin NF monograph. Discussion followed with the stakeholders.
  - The outcome of the discussion resulted in collaboration with FDA, industry and other stakeholders that was key to advancing the revision of the Gelatin NF.
  - These discussion were facilitated by open dialogue, information sharing
  - It is the first step to fuel the collaborative effort to update, modernize compendial standards.

Excipients Stakeholder Roundtable Discussion

Meeting #2 held a Stakeholder Roundtable Discussion –

"*Challenges to modernization and harmonization of USP-NF monographs when FCC and CFR specifications exist*"

Specific questions were discussed concerning the challenges to modernizing and harmonizing standards when regulatory and compendial standards both exist that are different.

- Communicate with and educate stakeholders on key issues relating to excipient monograph specifications so each can provide input into updating these standards
- Discuss differences that exist among Ph. Eur., *USP-NF*, FCC and US CFR
- Engage stakeholders in supporting revisions of excipient monographs

Outcome of the discussion: Excipient Project Team was formed

USP Excipient Stakeholder Project Team

- Date of initiation: August 19, 2014
- Charge:

  The purpose of this Project Team is to initiate a dialogue between stakeholders and USP regarding excipient modernization and informal harmonization to:

  - Identify and prioritize a list of USP-NF excipients that will benefit from both a modernized and harmonized monograph with other pharmacopoeias outside of the Pharmacopeial Discussion Group (PDG).
  - Identify key sponsors of these excipients who are willing to develop and submit a request for revision to both USP and other pharmacopeias outside of PDG.
  - Consider communication of Excipients Project Team-related initiatives to industry, regulatory, and other stakeholders including PDG.
  - Communicate with PDG on excipient monographs successfully completed by the Excipient Project Team for consideration of inclusion into the PDG workplan.
- Outcome:

  Completion of a list of USP-NF excipients identified by sponsors for modernization and informal harmonization with other pharmacopoeias outside PDG.

USP Excipient Stakeholder Project Team Members

- Chairs:
  - Current Chair: Priscilla S Zawislak (IPEC – Americas)
  - Current Chair: Steve Boudreau (GMIA) Served two Chair cycles
- Participating Organizations:
  - Gelatin Manufacturers Institute of America (GMIA)
  - International Minerals Association- North America (IMA-NA)
  - Institute of Shortening and Edible Oils
  - Corn Refiners Association
  - European Wax Federation
  - FDA
  - IPEC – Americas
  - IPEC – Europe
  - IPEC – China
  - GPhA
  - Mid west Compendial Discussion Group (MWCDG)
  - Western Compendial Discussion Group (WCDG)

Achievements

Excipients Project Team helps with the USP monograph up-to-date initiative:

Case study

1. Magnesium Aluminum Silicate
2. Gelatin

Case study #1: Magnesium Aluminum Silicate

Background and objective:

USP and US manufacturer of Magnesium Aluminum Silicate (MAS) identified tests for revision:

1) Strengthen the Identification

2) Bi-lateral Harmonization with Chinese Pharmacopeia (ChP) to include all 4 types of Magnesium Aluminum Silicate in the monograph

- Progress to Date:
- Visiting Scientist from ChP compared a list of high priority of USP and ChP monographs and made recommendations to include MAS in the list to modernize and harmonize with ChP.
- USP revision proposal is published in *Pharmacopeial Forum* 41(5). The revised monograph will be official in *USP39-NF34 2S* (Dec. 1, 2016)

Magnesium Aluminum Silicate (MAS) Comparison

Specification	ChP2015	USP38/NF33
Title	Aluminum Magnesium Silicate	Magnesium Aluminum Silicate
Definition	The ratio of aluminum content and magnesium content is 0.5-1.2.	<table><tr><th></th><th colspan="2">Viscosity (cps)</th><th colspan="2">Al Mg</th></tr><tr><th>Type</th><th>Min.</th><th>Max.</th><th>Min.</th><th>Max.</th></tr><tr><td>IA</td><td>225</td><td>600</td><td>0.5</td><td>1.2</td></tr><tr><td>IB</td><td>150</td><td>450</td><td>0.5</td><td>1.2</td></tr><tr><td>IC</td><td>800</td><td>2200</td><td>0.5</td><td>1.2</td></tr><tr><td>IIA</td><td>100</td><td>300</td><td>1.4</td><td>2.8</td></tr></table>
Description	+	+
Identification	(1) (2) (3) Wet Chemistry	X-RAY
Viscosity	20℃±0.1℃ is 0.3-0.6 Pa·S.	33 ± 3 ℃ Type IA: 225–600 Type IB: 150–450 Type IC: 800–2200 Type IIA: 100–300
pH/ Alkalinity	pH 9.0-10.0	pH 9.0–10.0
Acid demand	Not more than 4.0	NMT 4.0
Loss on drying	105℃, Not more than 8.0%	110℃ , NMT 8.0%
Loss on ignition	Lost not more than 17%	-
Heavy metals	Not more than 0.0015%.	-
Lead	-	NMT 15 μg/g
Arsenic	Not more than 0.0002%.	NMT 3 μg/g;
Microbial	Number of aerobic bacterial is not more than 1000 cfu/ g, number of fungi and yeast is not more than 100 cfu /g, Escherichia coli is not detected.	Total aerobic microbial count , not exceed 10^3 cfu/g, Absence of Escherichia coli.
ASSAY	Test method: Wet Chemistry	Test method: AA
Packaging and Storage		
Category		
Labeling		

Recommendation:

- It's reasonable to extend the scope of ChP monograph to include all 4 types

USP Visiting Scientist Program: ChP Visitors

- 2015/2016 USP Visiting Scientist for excipient projects:
- 2015 -First Visiting Scientist from the Comprehensive Department, China Pharmaceutical Packaging Association, Beijing, China
- 2016-Second Visiting Scientist from Jiangshu Institute of Food and Drug Control, Nanjing, China

http://www.usp.org/global/outreach-and-exchange-programs

USP Visiting Scientist Program: ChP Visitor

- From a list of 25 excipient monographs, 3 were selected for possible modernization and harmonization study.
- 3 additional monographs were added to the project.
  - Magnesium Aluminum Silicate (MAS)
  - Polyvinyl Alcohol (PVA)
  - Polysorbate 80
  - Sucrose
  - Ethylcellulose Aqueous Dispersion
  - Ethylcellulose Dispersion Type B

Case Study #2: Gelatin NF monograph

- **Background:**

- Food and Drug Administration (FDA) issued a guidance document entitled "Pharmaceutical Components at Risk for Melamine Contamination" on August 6, 2009 (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM175984.pdf)
- The Gelatin Manufacturer's Institute of America (GMIA) submitted the following laboratory study report and comments to FDA:
  - Melamine Spiking Technical Report – *"The Impact of Melamine Spiking on the Gel Strength and Viscosity of Gelatin"*
  - GMIA's Comments to FDA – Dec. 14, 2009
  - GMIA's Supplemental Comments to FDA – Oct. 16, 2012

Gelatin - FDA letter to USP, Dec. 2013

http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/2013-12-02_fda_mmtg_letter.pdf

- **FDA recommends USP add a new test(s) to ID section of Gelatin NF**

FDA has evaluated the melamine spiking study and other information submitted by GMIA and has conducted additional analytical studies to investigate further. The FDA studies include evaluations of several analytical methods to detect the presence of melamine spiked into samples of NF-grade gelatin. Two methods, powder x-ray diffraction (PXRD) and near-IR spectroscopy (NIRS), were found capable of producing accurate, quantitative measurement of melamine in gelatin in a reasonable timeframe, at levels greater than 1% w/w. More commonly-available methods found suitable of qualitative assessment of melamine in gelatin included Fourier transform infra-red (FT-IR) and Fourier transform Raman (FT-Raman) spectroscopy. This study data will be provided to you upon request.

We recommend that, as part of the general monograph modernization effort, USP consider adding a new analytical test or tests, as above, to the Gelatin, NF monograph. As noted in USP General Chapter <197>, IR and UV tests have general applicability to identification testing, and can be useful in detection of contaminants such as melamine. Additionally, we think that revision of the current *Identification* (Test B) might be useful so that it could qualitatively detect the presence of certain adulterants, such as melamine, that can alter the physico-chemical characteristics of gelatin.

Gelatin

- Research article from FDA

Cantor, Gupta, and Khan, JOURNAL OF PHARMACEUTICAL SCIENCES 103:539–544, 2014

- *"Analytical Methods for the Evaluation of Melamine Contamination"*

CONCLUSIONS

Because of the difference between the gelatin decomposition temperature and the melamine melting point, DSC could provide an initial screening for melamine in blends with gelatin, but would not be a good analytical technique to use. Several analytical techniques such as PXRD and NIRS were able to quickly and accurately assess the level of melamine contamination in gelatin blends at both high levels (>10%) indicative of deliberate adulteration or lower levels (<5%), possibly indicative of unintentional contamination. Both techniques can detect melamine at levels as low as 1% *w*/*w* and can be used to flag concern for a given product.

While chemometrics models were developed to analyze the NIRS, FT-Raman, and FT-infrared spectroscopic data, NIRS yielded the most accurate prediction model for determining the melamine level in gelatin blends. Although FT-Raman and FT-IR could not be used to accurately quantitate the melamine level, they can still be used to provide a qualitative assessment of product contamination. This analytical information will prove useful for future regulatory and pharmaceutical product quality issues related to melamine.

Step 1: Collaboration among stakeholders, USP and FDA

Objectives:

Develop a simple, cost-effective quality test to strengthen the Identification section by adding a more specific and sensitive test for Gelatin NF.

- GMIA Technical Committee met several times with USP
- USP also obtained feedback from the FDA
- GMIA members provided 33 samples of gelatin originating from various sources and of various grades.

Step 2: Collaboration among stakeholders, USP and FDA

- USP lab developed and validated the identification (ID) procedure for gelatin using diamond attenuated total reflection Fourier transform infrared spectroscopy (ATR FT-IR).
- The **sensitivity** of the procedure was evaluated with respect to **33** different gelatin test samples of various grade and animal origin from 5 manufacturers.
- The procedure's specificity and limit of **specificity** with respect to various concentrations of dry-blended melamine-adulterated gelatin samples was also determined.

Step 3: Current Status

- Gelatin Identification by Infrared (ID by IR) project has been successfully completed by USP.
- The ID by IR proposal has been accepted by USP Excipients Expert Committee for *PF* publication.
- FDA feedback was “this is a great example of collaborative efforts on monograph modernization”
- The Request for Revision to the harmonized Gelatin standard has been submitted and discussed by the Pharmacopeial Discussion Group (JP, EP, USP).
- USP plan to publish the revision proposal for ID by IR as USP local requirement through the regular revision pathway in *PF* 42(6) [Nov.-Dec., 2016]. The comment due date will be Jan. 31, 2017.

Acknowledgements

- USP Members

- GMIA Member Companies
  - Gelita
  - Nitta Gelatin
  - PB Leiner
  - Rousselot
  - Weishardt

Thank You